Renovascular Hypertension

To Stent or Not to Stent?

Patrick B. Mark, Ernesto L. Schiffrin, Garry L. Jennings, Anna F. Dominiczak, Ji-Guang Wang, Marc De Buyzere, Jan A. Staessen

Presentation of Case

A 69-year-old women smoker was referred to the nephrology clinic for assessment of hypertension and declining kidney function. At the time of referral, serum creatinine was 241 μmol/L and office blood pressure was 191/100 mm Hg. Her general practitioner had already performed 24-hour ambulatory monitoring and found no evidence of a white coat component to the hypertension. The patient was taking 4 antihypertensive agents (nifedipine long acting 60 mg daily, candesartan 32 mg daily, bisoprolol 10 mg daily, and bendroflumethiazide 2.5 mg daily). Serum creatinine was 110 μmol/L when last recorded, 1 year before referral. Physical examination was unremarkable with negative urinalysis for blood and protein.

E.L. Schiffrin: On the history, you have a smoker with impaired renal function and no proteinuria. I think this should evoke suspicions and I thought you should comment on it.

P.B. Mark: Absolutely. The diagnosis is clear that this is probably atherosclerotic renal artery disease. I don't think there is any debate on this. If there had been proteinuria, it would have opened up the diagnosis to all kinds of glomerulonephridities. We happened to have access to 1 test that day, the ultrasound test. That wouldn't have been the ideal test to seal the diagnosis.

G.L. Jennings: Was there an abdominal bruit? And would you like to comment on the usefulness of abdominal bruit?

P.B. Mark: I remember examining this lady and there was not an abdominal bruit. I also listened for femoral bruit. She did not have an abdominal or femoral bruit.[1]

Renal ultrasound revealed asymmetrical kidneys with the left kidney measuring 8.1 cm with loss of cortical tissue. The right kidney measured 11 cm and appeared normal. The positive smoking history, renal impairment, resistant hypertension, and asymmetrical kidneys on ultrasound were highly suggestive of renovascular disease.

E.L. Schiffrin: You mentioned already renal artery stenosis, so I can ask whether you see atherosclerotic renal artery stenosis, in the absence of smoking or diabetes mellitus or other causes of severe disseminated atherosclerosis?

P.B. Mark: I would say no in general, but I have just had a similar case referred to me, which I have yet to see. I think they may need more lipid work-up. It is surprising to see a 40-year-old nonsmoker referred with atherosclerotic renal artery disease.

Her referring physician debated whether further imaging was likely to lead to alteration in management. The rapid decline in kidney function in the presence of a normal-sized right kidney with preserved cortical tissue gave rise to the possibility of remediable critical right renal artery stenosis. We considered magnetic resonance angiography, computed tomographic angiography, and formal invasive renal angiography as imaging modalities for assessment of renal artery stenosis. Impaired renal function with estimated glomerular filtration rate 18 mL/min/1.73 m^2 is a relative contraindication for magnetic resonance angiography, in light of the risk of nephrogenic systemic fibrosis.[2] Therefore, computed tomographic angiography with prehydration was performed as first choice noninvasive imaging. Computed tomographic angiography confirmed the presence of a tight calcific ostial stenosis of right renal artery (arrowed), as well as moderately heavy aortic calcification and an atrophic left kidney (Figure 1)

Intervention With Renal Artery Stenting and Outcome

On the basis of declining kidney function, with resistant hypertension, in the presence of a critical stenosis to a single functioning kidney, we elected to proceed to renal artery intervention. The patient underwent renal artery CO_2 angiography with right renal artery angioplasty and stenting without complication (Figure 2).

For the subsequent days, there was a rapid normalization of renal function and substantial improvement in blood pressure, with creatinine falling to 92 μmol/L at 9 months post procedure. When most recently seen at clinic, 18 months post procedure, office blood pressure was well controlled (148/88 mm Hg) on 2 agents (bisoprolol and nifedipine) and serum creatinine was 122 μmol/L (estimated glomerular filtration rate 40 mL/min/1.73 m^2).

The slight dip in renal function at 18 months post procedure suggests the possibility of late in-stent restenosis, although no repeat imaging has been performed to date.[3] Even with this

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(*Hypertension*. 2014;64:1165-1168.)

***Hypertension* is available at http://hyper.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.114.04497

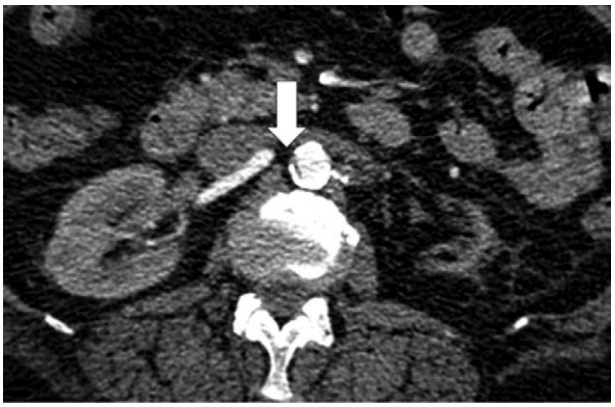

Figure 1. Computed tomographic renal angiography showing tight ostial right renal artery stenosis.

minor dip, it is clear that this case represents successful short- to medium-term outcome with renal artery angioplasty plus stenting for atherosclerotic renal artery stenosis. We will continue to work hard with the patient to address her other risk factors for atherosclerosis, including smoking cessation, treatment of dyslipidemia, and optimizing blood pressure control to try and protect the function of the single functioning kidney.

A.F. Dominiczak: Would you want to reimage and perhaps be ready to push the balloon across?

P.B. Mark: That is what we would like to do. However, the patient is extremely reluctant. And with the previous history of smoking and the several drugs, that is her choice. We would like to reimage. We had some debate with our radiologist because with the stent, we may have more difficulty imaging the stenosis and whether a straight angiogram might be better.

J.-G. Wang: You need to use ultrasound imaging to look at the change in the kidney and image the size of the kidney. That will tell us whether it is reversible or not reversible.

P.B. Mark: Yes, I think that is reasonable. If the kidney has become smaller or if the corticomedullary differentiation is less good, then it is possible to say that this may become less and less treatable.

E.L. Schiffrin: Have you succeeded in stopping her from smoking?

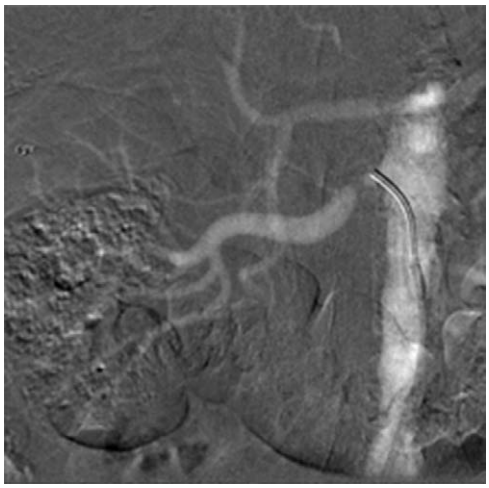

Figure 2. CO_2 renal angiography confirms the presence of right renal artery stenosis before angioplasty and stenting.

P.B. Mark: We have tried very, very hard. The answer is no. It makes you wonder about throwing all these treatments and exposing the patient to procedural risk as well.

Successful Result in the Context of Recent Clinical Trials

This successful result contrasts with recent well-conducted, high-profile randomized controlled trials of renal artery angioplasty and stenting compared with optimal medical therapy. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL),[4] Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL),[5] and Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR)[6] trials have consistently failed to show benefit with renal artery stenting compared with medical treatment, in terms of either patient survival, cardiovascular events, renal function, or blood pressure. ASTRAL, which was a global study, including several patients in Glasgow, randomized 806 patients with uni- or bilateral atherosclerotic renal artery stenosis to stenting or medical therapy and showed no difference in blood pressure, renal function, or progression to end-stage renal disease between the groups undergoing intervention compared with medical therapy. Renal artery stenting is not without risk, and in ASTRAL, serious adverse events directly related to renal revascularization were seen in 2.3% patients, including death and toe of limb amputation.[4] The smaller STAR trial compared renal artery stenting (64 patients) to medical therapy (76 patients) and showed no overall difference in progression of renal dysfunction between the groups.[6] More recently, CORAL, in North America, randomized 947 patients with atherosclerotic renal artery stenosis and either hypertension or chronic kidney disease to renal artery stenting or medical therapy. For a median of 43 months follow-up, there was no difference in the composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, congestive heart failure, progressive chronic kidney disease, or end-stage renal disease between the stented group and those treated with medical therapy.[5]

M. De Buyzere: Was she a good candidate to stent?

P.B. Mark: We had a good result. We have stented plenty over the years sometimes, with much poorer results. We would argue if ever there was a case for some benefit to be had, this was it. I do take your point. There was definitely established damage there, the renal function was poor, and the kidney was relatively small in size and there were other patient-related factors.

G.L. Jennings: As you just said, the results of the major trials in atherosclerotic renal artery stenosis have shown no benefit with the intervention over medical therapy. So that raises the question whether you went back a little bit further, would you really consider whether you should image her at all because medical therapy is what the guidelines are going to recommend.

This case demonstrates that there remains a group of patients who do benefit from stenting. Most clinicians accept that recurrent or flash pulmonary edema with preserved left ventricular systolic function in patients with renal artery stenosis

is an indication for renal angioplasty ± stenting.[7] Renal revascularization is unlikely to benefit patients with well-controlled blood pressure even on several agents and stable renal function. Small, shrunken kidneys have undergone irreversible ischemic damage, and functional improvement should not be anticipated with revascularization. Uncertainty remains in patients with renal artery disease and coexistent heart failure.[8] The patients enrolled in these admirable clinical trials cannot represent every clinical scenario, and it is inevitable that high-risk patients, similar to the case presented, present particular diagnostics challenges and may not have been randomized in large numbers to these trials.[9] Better characterization of the renal artery lesion using measures of fractional flow reserve may be helpful.[10] Alternatively, functional assessment of the kidneys for hibernating renal tissue, which may benefit from revascularization, has been described.[11] The results of these clinical trials should not deter clinicians from considering renal artery intervention, in carefully selected cases, where benefit is likely or the risks of stenting are outweighed by the likelihood of rapid progression to end-stage kidney disease in the absence of intervention.

Final Discussion of Hot Topics in Renal Artery Stenosis

A.F. Dominiczak: Can we go back to the picture with the narrowing and closing renal artery? There is a tiny, tiny flow there and it is about to close. What would happen next if nothing had been done? Well, I have had an identical patient. This was my first patient in the blood pressure unit many years ago, and we published this paper with Professor Chris Isles. What happened to the patient next was that she became anuric, the same age; everything was similar. She had malignant hypertension. She completely relied on the tiny bit of 1 closing renal artery. So this is a tightening stenosis to a sole kidney and next is dialysis. It is easy to criticize, but clearly 2 years later, this patient still does not need renal replacement therapy. So something has been achieved.

A. Brady (Glasgow): We had a lot of patients from our series in ASTRAL. For people who don't know how we recruited it; if a patient had a stenosis like this, they never went in the trial. They got angioplasty. For all the patients who had 50% to 60% stenosis, where you weren't sure, they sort of got put in the trial. I can't speak for CORAL, but I bet for the CORAL centers, which are mostly North American; those patients with really severe stenosis were never included in the studies. So those trials actually tell us nothing about critical stenosis, and I think for this individual there is clear benefit.

J. Dawson (Glasgow): I would support you. I would have referred that patient for stenting. If we were to go back in time, even with the trial data I would still refer that patient for stenting. I think the more interesting question is what would I do now? Now that the renal function has declined. And the question I have to help me make my mind up is: How much of the bounce in estimated glomerular filtration rate, the improvement, and subsequent change was because of perioperative stopping of the angiotensin receptor blocker and perhaps restarting or was therapy the same the whole way through?

P.B. Mark: The therapy was not the same. I can't answer the exact magnitude of each change, but the day post stenting, there was a drop in blood pressure. She had a torrential natriuresis and diuresis, blood pressure dropped, all drugs were stopped, then it was a labile evolving situation and it makes it extremely difficult to reinterpret what happened with the reintroduction of the drugs. But we didn't reintroduce an angiotensin receptor blocker because there was no other compelling reason to do so. Although I think reintroducing any antihypertensive drug will probably lead to a relative drop in the renal perfusion again. We don't know what her actual baseline is.

G.L. Jennings: Just a comment on the people with really tight stenosis didn't go into these trials, so we don't really know. CORAL did a retrospective subgroup analysis; those with a stenosis over 80% didn't show any different from those with a stenosis <80%. You probably need 80% for it to be functionally significant.

M. De Buyzere: For functional renal reserve, do you have a proposal for a cut-off where you should do it? For pressure-wire for instance.

P.B. Mark: I don't. For ASTRAL, I don't recall the exact entry criteria, but it was ≈50% to 70%. It was a less severe stenosis. We have no experience pressure-wiring. We have some experimental experience of doing magnetic resonance-perfusion renography, which has been published by the Manchester group.[12] It does look impressive for predicting response to renal revascularization, but we don't have a big enough case series of those. I think it comes back to the ultrasound actually. If they have a decent-size cortex and a reasonable-size kidney, there is a reasonable chance it might be a good outcome. If it's a 9 cm kidney or below, it's unlikely to be a good result. This was a 11 cm kidney, what if it had been a 10 cm kidney? I think it is difficult and that is where more data are required.

M. Walters (Glasgow): I am going to test Anna's earlier assertion that there are no stupid questions. Now that the renal function is deteriorating 9 months after the stent was inserted, the question is whether it is instant restenosis or not. What is the role or is there a potential role for contrast-free imaging, using for instance time of flight magnetic resonance angiography, which would obviate any risk of contrast-induced injury to the patient but may be sufficient to answer the specific question about the presence or absence of in-stent restenosis?

P.B. Mark: I'm not sure that is a stupid question. That is way over my head. Seriously, I think that with magnetic resonance angiography, time of flight imaging is a beautiful concept. But the artifact with magnetic resonance imaging relating to the actual stent itself is going to make this difficult. I don't have any experience with it.

J.A. Staessen: Why would you do the imaging again in this patient? Suppose you find out that the stent is thrombosed. What would you do?

P.B. Mark: I hope it is not thrombosed as the renal function would be considerably worse. I think that is an extremely difficult question to answer. If we find that there is a significant degree of in-stent restenosis, do we go back and subject the patient to another procedure and we will go round in the loop again?

E.L. Schiffrin: If we are spending so much money, or intend to, on this patient, why can't we spend a lot of money on stopping her from smoking? Surely, this has contributed to any additional vascular damage that has occurred since the recent intervention.

J.-G. Wang: How often do you see this kind of patient? If you see rarely, 1 or 2 patients a year, I think that is not a problem. We also had a similar case as you had with a rapid renal function decline. The severity of stenosis is not a good indicator, but rapid renal decline is a good indicator.

P.B. Mark: We don't look hard for renal artery stenosis beyond the clinical diagnosis. In the post-ASTRAL and post-CORAL age, we don't pursue renal artery stenting as aggressively as we did in the late 1990s and 2000s. I don't think we perform >≈5 or 10 a year. We used to do many more than this.

Acknowledgments

We thank Dr Colin C. Geddes, Dr Y. Mun Woo, Dr Kathryn K. Stevens (Nephrology), and Dr Iain Robertson (Interventional Radiology) for their help with management of this patient.

Disclosures

None.

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Hypertension
Journal of the American Heart Association

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Hypertension. 2014;64:1165-1168; originally published online September 22, 2014;
doi: 10.1161/HYPERTENSIONAHA.114.04497
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563